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Independent and Combined Effects of Heatwaves and $PM_{2.5}$ on Preterm Birth in Guangzhou, China: A Survival Analysis

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Background: Both extreme heat and air pollution exposure during pregnancy have been associated with preterm birth; however, their combined effects are unclear.

Objectives: Our goal was to estimate the independent and joint effects of heatwaves and fine particulate matter [PM <2.5 μm in aerodynamic diameter ($PM_{2.5}$)], exposure during the final gestational week on preterm birth.

Methods: Using birth registry data from Guangzhou, China, we included 215,059 singleton live births in the warm season (1 May–31 October) between January 2015 and July 2017. Daily meteorological variables from 5 monitoring stations and $PM_{2.5}$ concentrations from 11 sites were used to estimate district-specific exposures. A series of cut off temperature thresholds and durations (2, 3, and 4 consecutive d) were used to define 15 different heatwaves. Cox proportional hazard models were used to estimate the effects of heatwaves and $PM_{2.5}$ exposures during the final week on preterm birth, and departures from additive joint effects were assessed using the relative excess risk due to interaction (RERI).

Results: Numbers of preterm births increased in association with heatwave exposures during the final gestational week. Depending on the heatwave definition used, hazard ratios (HRs) ranged from 1.10 (95% CI: 1.01, 1.20) to 1.92 (1.39, 2.64). Associations were stronger for more intense heatwaves. Combined effects of $PM_{2.5}$ exposures and heatwaves appeared to be synergistic (RERIs >0) for less extreme heatwaves (i.e., shorter or with relatively low temperature thresholds) but were less than additive (RERIs <0) for more intense heatwaves.

Conclusions: Our research strengthens the evidence that exposure to heatwaves during the final gestational week can independently trigger preterm birth. Moderate heatwaves may also act synergistically with $PM_{2.5}$ exposure to increase risk of preterm birth, which adds new evidence to the current understanding of combined effects of air pollution and meteorological variables on adverse birth outcomes. https://doi.org/10.1289/EHP5117

Introduction

Preterm birth (PTB), defined as births with <37 completed gestational weeks, is a leading cause of death in children <5 years of age, responsible for approximately 1 million deaths in 2015 (Liu et al. 2016) and has been associated with long-term physical, cognitive, and developmental problems (Mwaniki et al. 2012; Saigal and Doyle 2008). There are approximately 14.84 million PTBs globally in 2014, with the total number of PTBs in China (approximately 1.17 million) ranked the second-highest (Chawanpaiboon et al. 2019).

Previous studies suggested that heat stress during pregnancy can induce the hypersecretion of antidiuretic hormone (ADH) and oxytocin (OT), or dehydration, which may decrease uterine blood flow and shift fetal metabolic pathways from anabolic to catabolic, resulting in the occurrence of PTB (Dreiling et al. 1991; Stan et al. 2013). An increasing number of epidemiological studies have reported that high-temperature exposure during very late gestation was associated with PTB (Basu et al. 2010; Ha et al. 2018; Schifano et al. 2013; Vicedo-Cabrera et al. 2015). Furthermore, some other studies have showed prolonged periods of high-temperature exposure, which was usually defined as a heatwave event, can significantly heighten the risk (Kent et al. 2014; Sun et al. 2019; Wang et al. 2013). In the context of climate change, the frequency and intensity of heatwaves are expected to increase (Hoegh-Guldberg et al. 2018; Schär 2016), which will accordingly add to the existing global PTB burden.

Meanwhile, climate change could affect human health indirectly through various pathways, for example, by deteriorating air quality (Watts et al. 2015). This is plausible because meteorological factors, including temperature, are implicated in ambient air pollutants' generation, transport, and possibly their toxicity (Gordon et al. 2014; Li et al. 2014; Tian et al. 2014). Zanobetti and Peters (2015) highlighted that the health impact associated with joint exposure to air pollution and extreme weather conditions can be larger than the risk estimated based on air pollution and weather alone. Kan et al. (2012) also stressed the importance of assessing the joint health impact of air pollution and climate

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change, especially in China, because the outdoor air pollution levels are particularly high in many Chinese cities.

The potential synergistic effects of temperature and air pollution have been studied mainly in the context of mortality or hospitalization rates. Several studies suggested that extreme temperatures and air pollution synergistically impact premature mortality (Benmarhnia et al. 2014; Li et al. 2017; Shaposhnikov et al. 2014) or hospital admissions for cardiovascular disease or respiratory outcomes (De Sario et al. 2013). Regarding PTB, previous studies have reported evidence of adverse effects of short-term (e.g., in the week prior to the delivery date) exposure to heatwaves (Kent et al. 2014; Sun et al. 2019; Wang et al. 2013) or fine particulate matter [PM <2.5 μm in aerodynamic diameter ($PM_{2.5}$)] alone (Guan et al. 2018; Huynh et al. 2006). However, whether heatwaves and $PM_{2.5}$ could also work synergistically to heighten PTB risk remains unclear.

To address this knowledge gap, we aimed to investigate the independent and possible interactive effects of heatwaves and $PM_{2.5}$ exposure on the risk of PTB using data from Guangzhou, China.

Methods

Population

The subjects for this retrospective cohort study were identified from the birth registry system in Guangdong province, China. More details about this system and population have been described in our previous studies (Wang et al. 2018, 2019). Briefly, we included mothers and their singleton live births in Guangzhou (total population ~14.5 million in 2017) from 1 January 2015 to 31 July 2017 ($N = 506{,}280$).

For a retrospective cohort study with a fixed study period based on the date of birth, a potential fixed cohort bias may occur when longer pregnancies are included at the start of the study and shorter pregnancies are included at the end of the study (Strand et al. 2011). In order to limit the potential for this bias, we only included women whose conception dates were between 28 weeks before the cohort started (1 January 2015), and 44 weeks before the cohort ended (31 July 2017) ($N = 470{,}192$) (Wang et al. 2018). We also excluded the births with outlier maternal ages (<13 or >50 y, $N = 39$) according to the average age at menarche (12.8 y) (Song et al. 2011) and natural menopausal age (50.8 y) (Shao et al. 2014) in the Chinese population. Compared with other PTBs, PTB with gestational age <28 weeks may have markedly different risk factors, among which infection was suggested to be the most important contributor (Moutquin 2003); therefore, these PTBs ($N = 178$, 0.04% of the total births) were excluded.

Some previous studies have suggested that exposure to heatwaves in the week prior to the delivery date can trigger PTB (Kent et al. 2014; Sun et al. 2019; Wang et al. 2013). Because it is not clear that earlier exposures could directly trigger labor via thermoregulatory mechanisms (Auger et al. 2014), we restricted the exposure window to the final gestational week and so included only births that occurred during the warm season (1 May–31 October, $N = 249{,}489$). In Guangzhou, which has a subtropical climate, these months are the warmest of the year (Sheng et al. 2018).

Collected variables included each woman's home address during pregnancy (at district level), maternal age, parity, medical conditions during pregnancy [i.e., an indicator (yes/no) of any such conditions as placental abruption, placenta previa, placental accreta, pregnancy-induced hypertension, preeclampsia, eclampsia, oligohydramnios, uterine rupture, and gestational diabetes], delivery method, gestational age, date of birth, birth weight, and sex of infant. There were missing data on medical conditions during pregnancy (14.0%), parity (13.8%), and delivery method (13.8%). In the following data analyses, medical conditions during pregnancy and delivery method were not included as covariates in the models because pregnancy complications (e.g., preeclampsia) are on the causal pathway of antenatal exposure and birth outcomes and that adjustment for these variables in the model may result in overadjustment (Ananth and Schisterman 2017; Schisterman et al. 2009), and delivery method may not meet the generally accepted definition of a confounder affecting both the outcome and the exposure without being a cause of the exposure. Parity was treated as a covariate, and in order to rule out the potential influence of the missing data, we excluded all cases with missing parity to conduct complete case analysis. The final sample size for the analysis comprised 215,059 births.

This study was approved by the medical ethics committee of the School of Public Health, Sun Yat-sen University. Data used in the study were anonymous and included no individually identifiable information.

Preterm Birth Outcomes

The gestational age (in weeks) was determined by combining ultrasound examination and mother-reported last menstrual period to represent the best available clinical estimate for each woman. When available, ultrasound estimates were used; otherwise, the date of the last menstrual period was used. The newborns included in this study covered deliveries in hospitals (93.09–99.98% across districts), maternity and child care institutions (0–6.77%), and at homes or other nonmedical facilities (0–0.22%). For those delivered in hospitals or maternity and child care institutions, they usually received antenatal care and gestational age was determined by ultrasound examination in the first or second trimester (Fu and Yu 2011).

PTB was defined as delivery prior to 37 completed weeks of gestation (Beck et al. 2010). According to World Health Organization recommendations (WHO 2019), PTB can be further classified into moderate-to-late PTB (32 to before 37 completed weeks), very PTB (28 to before 32 completed weeks), and extremely PTB (less than 28 completed weeks). In our study population, we included only very and moderate-to-late PTBs. Owing to the low number of very PTBs ($N = 807$) and referring to a previous study (Basu et al. 2010), we subclassified PTBs into earlier PTB (weeks 28–34, $N = 3{,}416$) and later PTB (weeks 35–36, $N = 7{,}693$) to allow for sufficient earlier PTB cases and to evaluate whether the effects of heatwaves and $PM_{2.5}$ exposure varied by gestational age.

Heatwave Exposure Assessment

Meteorological variables, including daily mean and maximum temperature [in degrees Celsius (°C)] as well as relative humidity (%) from five meteorological stations, were collected from Guangdong Meteorological Service Center (http://gd.cma.gov.cn/). As Figure S1 shows, among 11 geographic districts, each of three districts (Huadu, Conghua, and Zengcheng) has one monitoring station. Meteorological variables collected from each station were used to represent the exposure of the pregnant women living in the same district during pregnancy. For other districts, the women living in different but proximate districts shared the data from one station. In this study, the women in Nansha and Panyu shared the data from one station, and the data from the remaining station was used to represent the exposure of women in Haizhu, Liwan, Huangpu, Yuexiu, Baiyun, and Tianhe districts.

There is no universally consistent heatwave definition. Heatwave metrics and effects on health can be regionally specific depending on the prevailing local climate (Kent et al. 2014; Xu et al. 2016). Existing studies have usually used a series of temperature thresholds (absolute or percentiles) and durations to define heatwaves (Xu et al. 2016). In our study location, some previous studies (He et al. 2016; Liang et al. 2016) evaluated high-temperature exposure and PTB, but the duration of hot days was not considered in their studies. Therefore, no clear evidence on appropriate absolute temperatures was available for us to define heatwaves.

Given that the mean daily maximum temperature during the warm season (May–October) was 32.2°C, we first used a slightly higher absolute temperature (33°C, 55th percentile of daily maximum temperature during the study period) as a threshold to define heatwaves with daily maximum temperature ≥33°C for at least 2, 3, or 4 consecutive d (denoted as 33°C-D2, 33°C-D3, 33°C-D4). Then, informed by previous studies (Wang et al. 2013; Xu et al. 2016), higher temperature thresholds corresponding to the 75th (34.6°C), 90th (35.7°C), 95th (36.4°C), and 98th (37°C) percentiles of daily maximum temperature during the study period and lasting for at least 2, 3, or 4 consecutive d were also used to define heatwaves [denoted as 75th-D2, 75th-D3, 75th-D4, 90th-D2, 90th-D3, 90th-D4, 95th-D2, 95th-D3, 95th-D4, 98th-D2, 98th-D3, and 98th-D4 (Table 1)]. For each mother, we calculated the number of heatwaves (using each definition above) they experienced in the last gestational week before delivery. The number of PTBs experiencing heatwaves under definitions of 95th-D4, 98th-D3, and 98th-D4 were 38, 38, and 11, respectively. Due to the limited number of events, we did not include these heatwaves in the final analyses.

Air Pollution Exposure Assessment

The air pollution exposure assessment for each pregnancy, based on district-specific exposure estimates, was reported in our previous study (Wang et al. 2018, 2019). In brief, there are 11 geographic districts and 11 air quality monitoring stations operated by the State Environmental Protection Administration of China in Guangzhou (see Figure S1). From each station, we collected daily ambient air pollutant concentrations (in micrograms per cubic meter) for the entire study period, including PM <10 μm micrometers in aerodynamic diameter (PM_{10}), $PM_{2.5}$, nitrogen dioxide (NO_2), sulfur dioxide (SO_2), and ozone (O_3) (daily maximum 8-h average level), and then assigned them as the daily exposure for each woman living in the same district during pregnancy. Haizhu and Huangpu districts had two stations each and so the average concentration was calculated. Nansha and Zengcheng districts did not have a station, so air pollution concentrations from the nearest station in Panyu and Huangpu districts, respectively, were used.

Very few air pollution observations (0.51–1.98%) were missing during the study period. We imputed a daily missing value with the mean of the two closest values within 7 d before and after the missing data (Wang et al. 2018). After the imputation, there were no missing values. We then derived weekly air pollution exposure estimates for each pregnancy, from the week of conception to the week of delivery.

Statistical Analyses

Basic risk models. In the present study, we first built the basic risk models, which included all covariates other than heatwave and $PM_{2.5}$ exposure in the last gestational week before delivery. We fitted Cox proportional hazard models to estimate the hazard of PTB during each completed gestational week *t*, by treating PTB as a time-to-event outcome with term births censored at week 37 (Wang et al. 2013).

$$h[t, X_I, X_i(t)] = h_0(t)\exp[\beta_I X_I + \beta_d X_i(t)], \tag{1}$$

where $h_0(t)$ is the baseline hazard function, indicating the hazard function for an individual with all variables equal to zero; X_I refers to the values of time-independent variables during pregnancy, including maternal age, parity, and month of birth. Relative humidity exposure in the last gestational week before delivery was also controlled for. Residency districts of the participants were included as a random effect. $X_i(t)$ are the values of the time-varying variables during pregnancy, including longer-term gestational temperature and $PM_{2.5}$ exposure, defined as the exposure across the entire pregnancy except for the last gestational week before delivery. The exposure is from week 1 to *t*-1 for PTBs, whereas for term births the exposure is from week 1 to 36 because all term births are censored at week 37.

Weekly mean temperatures were averaged across the above-mentioned longer-term gestational period and included in the models as a natural cubic spline with three degrees of freedom (dfs) (Wang et al. 2018). Some previous studies have suggested that the effects of gestational $PM_{2.5}$ exposures on PTB varied at a weekly level (Sheridan et al. 2019; Wang et al. 2018). In the models, $X_i(t)$ for $PM_{2.5}$ were treated as a cross-basis function combining the exposure–response and lag–response function in a distributed lag model (DLM) (Gasparrini 2014; Wang et al. 2018). We used a linear function to model the exposure–response

Table 1. Characteristics of heatwave events and individual-experienced heatwaves in the warm season (May–October) in Guangzhou, China, 2015–2017.

	Heatwave definitions	Cut off percentile and temperature (°C)	Duration (d)	Heatwave events (n)[a]	Participants who experienced heatwave (n)[b]	Preterm births that experienced heatwave (n)[b]	Participants who experienced >1 heatwave (n)[c]
1	33°C-D2	55th (33.0)	2	194	112,443	5,754	6,856
2	33°C-D3	55th (33.0)	3	164	84,334	4,399	601
3	33°C-D4	55th (33.0)	4	124	56,756	3,056	0
4	75th-D2	75th (34.6)	2	137	63,638	3,538	2,682
5	75th-D3	75th (34.6)	3	98	44,442	2,550	395
6	75th-D4	75th (34.6)	4	66	25,918	1,458	0
7	90th-D2	90th (35.7)	2	71	30,854	1,766	1,199
8	90th-D3	90th (35.7)	3	49	17,280	982	61
9	90th-D4	90th (35.7)	4	22	4,921	263	0
10	95th-D2	95th (36.4)	2	43	18,211	1,033	595
11	95th-D3	95th (36.4)	3	19	4,053	224	0
12	95th-D4	95th (36.4)	4	5	828	38	0
13	98th-D2	98th (37.0)	2	17	4,556	264	57
14	98th-D3	98th (37.0)	3	5	757	38	0
15	98th-D4	98th (37.0)	4	2	275	11	0

Note: Heatwaves were defined by an absolute (33°C) or percentile temperature threshold (75th, 90th, 95th, 98th percentiles, corresponding to 34.6°C, 35.7°C, 36.4°C, and 37°C, respectively) and by the number of consecutive days above the threshold (2–4 d, indicated by D2, D3, or D4).
[a]Number of heatwave events during the warm season (May–October) of the study period (2015–2017).
[b]Number of the total participants and preterm births that experienced at least one heatwave in the last gestational week before delivery.
[c]Number of pregnant women who experienced more than one heatwave in the last gestational week before delivery.

relationship between weekly $PM_{2.5}$ exposures and PTB, and we then applied natural cubic splines to model the lag distribution of the weekly effects. Given that term births were censored at week 37, we set 36 weeks as the maximum lag range. By varying dfs from 3 to 10 (knots were set equally spaced), an optimal lag distribution with dfs of 7 was selected based on the minimum Akaike information criterion (AIC) (Gasparrini 2014).

We built similar basic risk models for earlier PTB (weeks 28–34) and later PTB (weeks 35–36) as we did for overall PTB. For earlier PTB, gestational temperature and $PM_{2.5}$ exposure was restricted to exposure from week 1 to 33 for term births and from week 1 to t-1 for PTBs.

Independent effects of heatwave and $PM_{2.5}$ exposure on PTB. Based on the basic risk models, we added heatwave and $PM_{2.5}$ exposures during the last week before delivery to estimate their independent effects.

$$h[t, X_I, X_i(t)] = h_0(t)\exp\left[\beta_I X_I + \beta_d X_i(t) + \beta_{HW} X_{HW_n} + \beta_{PM2.5} X_{PM2.5}\right], \tag{2}$$

where X_{HW_n} and $X_{PM2.5}$ refer to a heatwave definition n and $PM_{2.5}$ exposure during the last week before delivery, respectively. Few women ($N = 0$–6,856, accounting for 0–3.19% of the total women included) experienced more than one heatwave during the last week of gestation (Table 1). Therefore, we assigned exposure to a heatwave under each definition n as a binary value (yes/no), which indicated whether or not the pregnant women experienced at least one heatwave event in the last gestational week before delivery. The last week's average $PM_{2.5}$ exposure was included as a continuous variable, with the hazard ratios (HRs) and 95% confidence intervals (CIs) calculated per 10-$\mu g/m^3$ increase in $PM_{2.5}$ concentration.

Interactive effects of heatwave and $PM_{2.5}$ exposure on PTB. We evaluated whether the combined effects of heatwaves and $PM_{2.5}$ exposure during the last gestational week on PTB were more or less than additive, which may be more informative for translating epidemiological results into public health actions than departures from multiplicative risks (indicated by the product interaction term in Cox models) (Rothman 2002). Specifically, we calculated the relative excess risk due to interaction (RERI) (VanderWeele and Knol 2014), where an RERI of 0 indicates additive risks (i.e., the absence of an additive interaction), an RERI >0 indicates combined effects of heatwaves and $PM_{2.5}$ on PTB that are greater than expected (i.e., synergistic) based on the estimated effects of each exposure alone, and an RERI <0 indicates less than additive joint effects.

Furthermore, in order to present the magnitude of the joint associations in a more straightforward manner, as well as to test the robustness of interactions estimated by treating $PM_{2.5}$ as a continuous metric, we used the 50th percentile of $PM_{2.5}$ concentrations in the last gestational week as a cut off to classify $PM_{2.5}$ into a binary variable ($\geq 29.6\ \mu g/m^3$ and $< 29.6\ \mu g/m^3$). The above-mentioned models were then used to estimate the effects of several combinations of heatwaves and $PM_{2.5}$ exposure: *a*) heatwave and $PM_{2.5} < 29.6\ \mu g/m^3$, *b*) no heatwave and $PM_{2.5} \geq 29.6\ \mu g/m^3$, *c*) heatwave and $PM_{2.5} \geq 29.6\ \mu g/m^3$, and using the combination of *d*) no heatwave and $PM_{2.5} < 29.6\ \mu g/m^3$ as a reference group. We also calculated RERIs based on the method described by Hosmer and Lemeshow (1992). To allow for a sufficient sample size in each subgroup, only heatwaves based on nine definitions (33°C-D2, 33°C-D3, 33°C-D4, 75th-D2, 75th-D3, 75th-D4, 90th-D2, 95th-D2, and 98th-D2) were used.

Sensitivity Analyses

We performed a number of sensitivity analyses to test the robustness of our results. To examine the impact of adjusting for confounding, we repeated all analyses without adjusting for maternal age, parity, month of birth, and relative humidity exposure in the last gestational week before delivery. It should be noted that, even in these unadjusted models, the natural cubic spline of mean gestational temperature and the cross-basis function of gestational $PM_{2.5}$ exposures were still included so that the short-term effects could be isolated. In our previous study, we found that gestational exposure to $PM_{2.5}$ (weeks 20–28) was associated with increased PTB risk (Wang et al. 2018). Therefore, we repeated models after adjusting for average $PM_{2.5}$ exposure during weeks 20–28, instead of using a cross-basis function, to estimate the effects of heatwaves and $PM_{2.5}$ on PTB. Some previous studies (Lee et al. 2013; Zhao et al. 2015) have reported that air pollution or extreme temperature may have different effects on spontaneous and medically indicated PTB. We did not have information to distinguish between these PTB subtypes in our study population but, instead, performed analyses stratified by delivery method (vaginal or Cesarian birth).

All analyses were performed with SAS (version 9.4; SAS Institute, Inc.) and R (version 3.4.4; R Development Core Team), and packages dlnm, splines, survival, and epiR in R software were used (Gasparrini 2014; Hosmer and Lemeshow 1992).

Results

As Table 1 shows, during the warm season (May–October) of the study period, the maximum number of heatwave events using different heatwave definitions was 194 [daily maximum temperature ≥33°C (the 55th percentile) lasting for at least 2 d] and the minimum number was 2 [daily maximum temperature ≥37°C (the 98th percentile) lasting for at least 4 d]. This corresponded to 112,443 and 275 pregnant women experiencing at least one heatwave during the final gestational week before delivery, respectively.

Of the 215,059 singleton live births included in the study, 11,109 (5.17%) were PTBs. The number of PTBs during heatwaves ranged from 11 [daily maximum temperature ≥37°C (the

Table 2. Summary statistics of births in the warm season (May–October) in Guangzhou, China, 2015–2017.

Characteristics	Preterm births $n = 11{,}109$	Term births $n = 203{,}950$	Total births $n = 215{,}059$
Gestational age [weeks (mean ± SD)]	34.7 ± 1.8	39.0 ± 1.1	38.7 ± 1.4
Maternal age [y (mean ± SD)]	29.5 ± 5.4	28.6 ± 5.0	28.7 ± 5.0
Month of birth [n (%)]			
May	2,643 (23.8)	48,805 (23.9)	51,448 (23.9)
June	1,832 (16.5)	44,733 (21.9)	46,565 (21.7)
July	1,831 (16.5)	31,376 (15.4)	33,207 (15.4)
August	1,796 (16.2)	29,590 (14.5)	31,386 (14.6)
September	1,536 (13.8)	24,125 (11.8)	25,661 (11.9)
October	1,471 (13.2)	25,321 (12.4)	26,792 (12.5)
Parity [n (%)]			
Primiparous	5,023 (45.2)	94,369 (46.3)	99,392 (46.2)
Multiparous	6,086 (54.8)	109,581 (53.7)	115,667 (53.8)
Medical condition during pregnancy [n (%)][a]			
No	2,218 (20)	116,773 (57.3)	118,991 (55.3)
Yes	8,881 (79.9)	86,587 (42.5)	95,468 (44.4)
Missing	10 (0.1)	590 (0.3)	600 (0.3)
Delivery method [n (%)]			
Vaginal	6,196 (55.8)	137,224 (67.3)	143,420 (66.7)
Cesarean	4,913 (44.2)	66,726 (32.7)	71,639 (33.3)
Infant sex [n (%)]			
Male	6,607 (59.5)	108,506 (53.2)	115,113 (53.5)
Female	4,502 (40.5)	95,444 (46.8)	99,946 (46.5)

Note: SD, standard deviation.

[a]Medical condition during pregnancy was collected as an indicator of any conditions, including placental abruption, placenta previa, placental accreta, pregnancy-induced hypertension, preeclampsia, eclampsia, oligohydramnios, uterine rupture, and gestational diabetes.

98th percentile) for at least 4 consecutive d] to 5,754 [daily maximum temperature ≥33°C (the 55th percentile) for at least 2 consecutive d] (Table 1).

Table 2 shows the summary characteristics of the study population. Older mothers were more likely to have PTBs. Compared with term births, PTBs were observed more frequently among multiparous mothers, male babies, and Cesarean deliveries. The proportion of women with a medical condition during pregnancy was 79.9% among PTBs, which was higher than that among term births (42.5%).

In the study period, the mean concentration of $PM_{2.5}$ was $29.8\ \mu g/m^3$ (SD = 14.7) and the mean daily maximum temperature was 32.2°C (SD = 3.0) (see Table S1). $PM_{2.5}$ was moderately to highly correlated with PM_{10}, NO_2 and O_3. When restricted to the exposure during the last week before delivery for all pregnancies (see Table S2), the mean concentration of $PM_{2.5}$ was $30.5\ \mu g/m^3$ (SD = 9.4), and the mean daily maximum temperature was 31.8°C (SD = 2.1). The correlations among pollutants and meteorological factors were very similar to the study period as a whole. Because this research focused on exposure during the last week prior to delivery, we also calculated the Pearson's correlation coefficient for average temperature and $PM_{2.5}$ between exposure during the entire pregnancy and during the last week (see Table S3). We observed a weak and negative correlation for both temperature ($r = -0.18$) and $PM_{2.5}$ ($r = -0.07$). On average, the $PM_{2.5}$ concentration in the last gestational week for women experiencing at least one heatwave was higher than that for women experiencing none (see Table S4).

Figure 1 shows the HRs and 95% CIs of PTB for the women who experienced at least one heatwave in the last week before delivery. Except for 33°C-D2 and 33°C-D3, the rest of the 10 different heatwave definitions used to estimate effect were associated with a higher risk of PTB. The HRs (95% CIs) of PTB ranged from 1.10 (95% CI: 1.01, 1.20) to 1.92 (1.39, 2.64). In general, the risk of PTB increased with the intensity of heatwave, (i.e., HRs increased with higher temperature thresholds or longer durations).

When all covariates were removed from the models except for gestational temperature and $PM_{2.5}$ exposure, associations with heatwaves decreased slightly compared with the adjusted estimates (Figure 1), and HRs for 33°C-D3 and 90th-D4 became nonsignificant. When stratified by gestational age (Figure 2), all

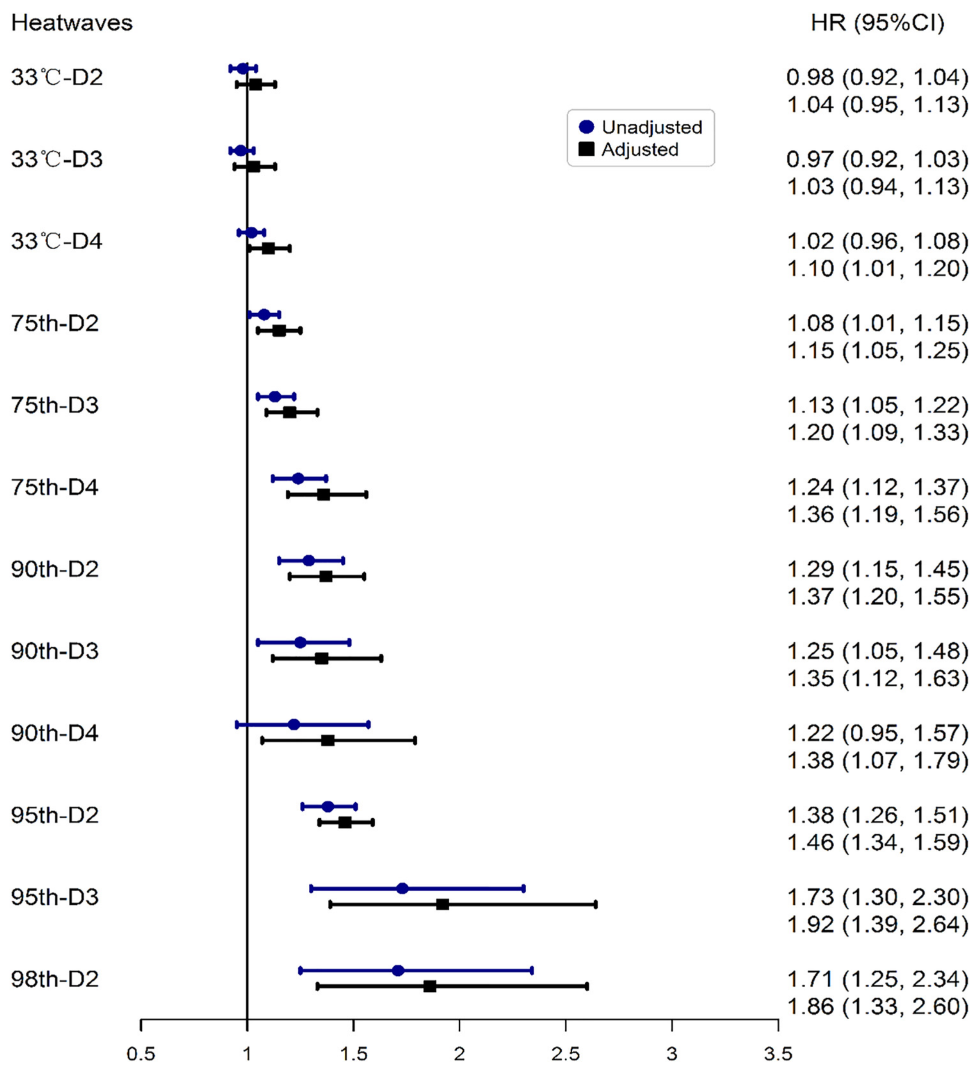

Figure 1. Hazard ratios of preterm birth associated with heatwave exposure in Guangzhou, China, 2015–2017. Heatwaves were defined by an absolute (33°C) or percentile temperature threshold (75th, 90th, 95th, 98th percentiles, corresponding to 34.6°C, 35.7°C, 36.4°C, and 37°C, respectively) and by the number of consecutive days above the threshold (2–4 d, indicated by D2, D3, or D4); Unadjusted model included only gestational temperature, gestational and the last week $PM_{2.5}$ exposures; residency districts of the participants were fitted as a random effect. Adjusted model additionally included maternal age, parity, month of birth, and relative humidity in the last gestational week before delivery. Note: CI, confidence interval; HR, hazard ratio.

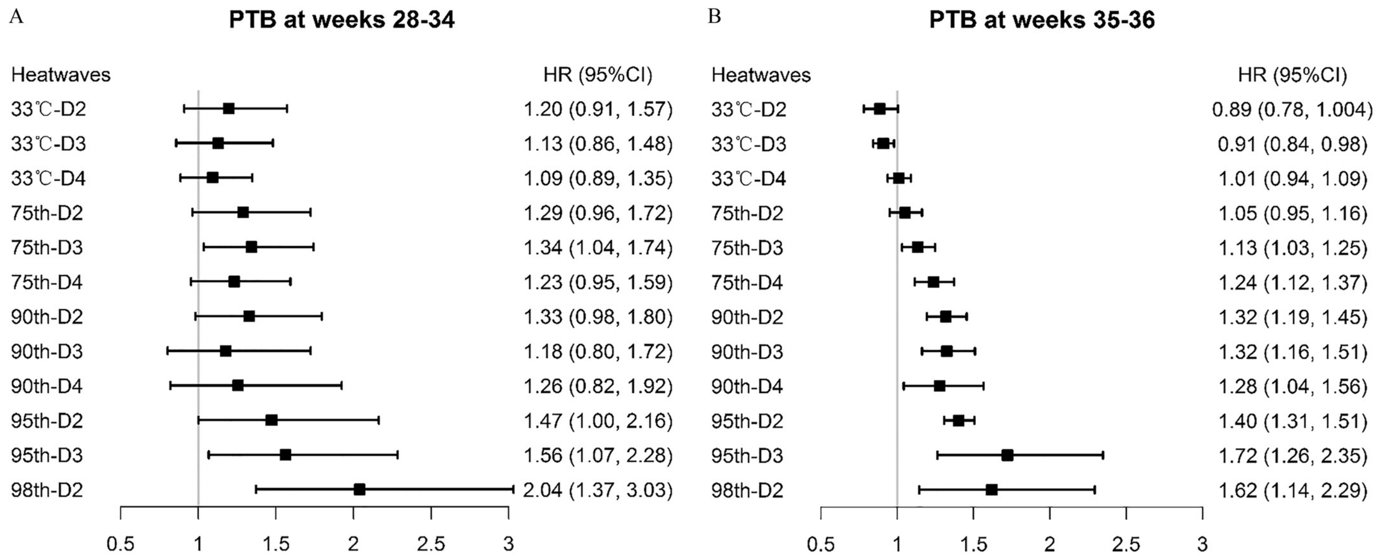

Figure 2. Hazard ratios of preterm birth associated with heatwave exposure, for preterm birth at (A) weeks 28–34 and (B) weeks 35–36 in Guangzhou, China, 2015–2017. Heatwaves were defined by an absolute (33°C) or percentile temperature threshold (75th, 90th, 95th, 98th percentiles, corresponding to 34.6°C, 35.7°C, 36.4°C, and 37°C, respectively) and by the number of consecutive days above the threshold (2–4 d, indicated by D2, D3, or D4). Models included gestational temperature, gestational and the last week $PM_{2.5}$ exposures, maternal age, parity, month of birth, and relative humidity in the last gestational week before delivery; residency districts of the participants were fitted as a random effect. Note: CI, confidence interval; HR, hazard ratio.

heatwaves that were more intense than 75th-D2 were associated with a higher risk of PTB at 35–36 weeks, with HRs (95% CIs) ranging from 1.13 (1.03, 1.25) to 1.72 (1.26, 2.35). However, for PTB at 28–34 weeks, very intense heatwaves (95th-D2, 95th-D3, 98th-D2) were associated with PTB.

All HRs for PTB in association with a 10-$\mu g/m^3$ increase in $PM_{2.5}$ exposure during the last gestational week were positive but nonsignificant (see Table S5). Effect estimates from adjusted models were slightly higher than unadjusted estimates. When stratified by gestational age, associations between $PM_{2.5}$ exposures and PTB were stronger for PTB at weeks 35–36 of gestation compared with PTB at weeks 28–34.

Although RERIs for additive interactions were not significant (i.e., 95% CIs contained 0), we observed an interesting interaction pattern (Table 3). For overall PTB, estimates suggested a synergistic effect (RERI > 0) of less intense heatwaves and $PM_{2.5}$ exposure, whereas for more intense heatwaves (90th-D3, 90th-D4, 95th-D2, 95th-D3, 98th-D2) the RERIs were < 0, suggesting that joint effects were less than expected for additive risks. The pattern was similar in unadjusted models, and for later PTBs. For earlier PTBs, all RERIs were > 0, suggesting a synergistic effect of heatwaves and $PM_{2.5}$ exposure.

When $PM_{2.5}$ exposure in the last gestational week was treated as a binary variable ($\geq 29.6\ \mu g/m^3$ and $< 29.6\ \mu g/m^3$), we also observed evidence of greater than additive risks for high $PM_{2.5}$ and moderately intense heatwaves, but not for more intense heatwaves (Table 4). For example, among overall PTBs, we found evidence of significant synergistic effects for 33°C-D2, 33°C-D3, and 75th-D3 heatwaves with high $PM_{2.5}$ exposure ($\geq 29.6\ \mu g/m^3$), with RERIs from adjusted models of 0.26 (95% CI: 0.12, 0.39), 0.24 (95% CI: 0.09, 0.40), and 0.40 (95% CI: 0.02, 0.78) respectively, suggesting 26%, 24%, and 40% excess risks relative to expectations based on the independent effects estimated for each exposure alone.

In sensitivity analyses, associations between heatwaves and overall PTB were slightly stronger when we adjusted for average $PM_{2.5}$ exposure during weeks 20–28 instead of average $PM_{2.5}$ during the entire pregnancy and the last week of gestation (see Table S6). When the analyses were stratified by delivery method

Table 3. Relative excess risk due to interaction of heatwave and $PM_{2.5}$ exposure on preterm birth in Guangzhou, China, 2015–2017.

	Overall PTB[a]		Overall PTB[b]		PTB at weeks 28–34[b]		PTB at weeks 35–36[b]	
Heatwaves	Unadjusted RERI	95% CI	Adjusted RERI	95% CI	RERI	95% CI	RERI	95% CI
33°C-D2	2.33	−0.46, 5.11	2.43	−0.45, 5.31	0.78	−0.57, 2.13	0.94	−0.71, 2.59
33°C-D3	1.70	−0.43, 3.82	1.66	−0.50, 3.83	1.30	−0.95, 3.55	0.59	−0.50, 1.69
33°C-D4	0.91	−1.36, 3.17	0.89	−1.73, 3.52	1.50	−0.37, 3.38	0.19	−1.71, 2.09
75th-D2	1.88	−1.83, 5.59	1.81	−2.18, 5.80	0.87	−0.14, 1.88	0.41	−2.35, 3.18
75th-D3	2.31	−2.59, 7.20	2.15	−2.89, 7.19	0.84	−0.20, 1.89	0.94	−2.90, 4.78
75th-D4	1.64	−2.37, 5.64	1.35	−2.76, 5.47	1.65	−0.41, 3.72	0.33	−2.81, 3.47
90th-D2	0.49	−3.88, 4.86	0.15	−4.53, 4.83	1.62	0.07, 3.17	−1.28	−3.79, 1.24
90th-D3	−0.74	−3.13, 1.66	−1.10	−3.90, 1.71	2.64	−0.41, 5.69	−1.9	−3.74, −0.05
90th-D4	−1.67	−4.30, 0.96	−1.89	−5.28, 1.51	2.53	−2.15, 7.22	−1.66	−4.73, 1.40
95th-D2	−0.64	−2.98, 1.69	−1.07	−3.89, 1.75	1.05	−0.15, 2.25	−2.24	−4.11, −0.37
95th-D3	−11.2	−21.27, −1.14	−14.4	−27.46, −1.33	9.62	−7.71, 26.95	−9.83	−23.43, 3.77
98th-D2	−6.85	−13.93, 0.23	−8.64	−17.46, 0.19	10.99	−18.51, 40.50	−5.76	−13.63, 2.10

Note: Heatwaves were defined by an absolute (33°C) or percentile temperature threshold (75th, 90th, 95th, 98th percentiles, corresponding to 34.6°C, 35.7°C, 36.4°C, and 37°C, respectively) and by the number of consecutive days above the threshold (2–4 d, indicated by D2, D3, or D4); $PM_{2.5}$ exposure in the last gestational week was included in each model as a continuous variable. Each RERI was calculated for per 10-$\mu g/m^3$ increment in $PM_{2.5}$ with each heatwave exposure. CI, confidence interval; $PM_{2.5}$, particulate matter < 2.5 μm in aerodynamic diameter; PTB, preterm birth; RERI, relative excess risk due to interaction.

[a]Unadjusted model included only gestational temperature and $PM_{2.5}$ exposures; residency districts of the participants were fitted as a random effect.

[b]Adjusted model additionally included maternal age, parity, month of birth, and relative humidity in the last gestational week before delivery.

Table 4. Hazard ratios and relative excess risk due to interaction of heatwave and $PM_{2.5}$ exposure on preterm birth in Guangzhou, China, 2015–2017.

		Overall PTB[c]		Overall PTB[d]		PTB at weeks 28–34[d]		PTB at weeks 35–36[d]	
Heatwaves[a]	$PM_{2.5}$ ($\mu g/m^3$)[b]	Unadjusted HR	95% CI	Adjusted HR	95% CI	HR	95% CI	HR	95% CI
33°C-D2									
No	<29.6	1.00	—	1.00	—	1.00	—	1.00	—
No	≥29.6	1.09	0.82, 1.45	1.09	0.81, 1.47	1.00	0.72, 1.39	1.19	0.91, 1.57
Yes	<29.6	0.89	0.80, 0.99	0.94	0.82, 1.07	1.17	0.92, 1.49	0.88	0.74, 1.04
Yes	≥29.6	1.22	0.91, 1.65	1.29	0.97, 1.71	1.24	1.00, 1.54	1.10	0.86, 1.40
RERI		0.25	0.09, 0.40	0.26	0.12, 0.39	0.08	−0.24, 0.39	0.03	−0.12, 0.18
33°C-D3									
No	<29.6	1.00	—	1.00	—	1.00	—	1.00	—
No	≥29.6	1.12	0.84, 1.51	1.13	0.84, 1.52	1.03	0.75, 1.41	1.18	0.88, 1.57
Yes	<29.6	0.89	0.82, 0.97	0.95	0.84, 1.06	1.16	0.91, 1.47	0.87	0.77, 0.98
Yes	≥29.6	1.25	0.91, 1.74	1.32	0.96, 1.81	1.16	0.95, 1.41	1.15	0.84, 1.58
RERI		0.24	0.08, 0.40	0.24	0.09, 0.40	−0.03	−0.38, 0.33	0.10	−0.04, 0.24
33°C-D4									
No	<29.6	1.00	—	1.00	—	1.00	—	1.00	—
No	≥29.6	1.18	0.91, 1.54	1.18	0.90, 1.55	1.02	0.80, 1.30	1.21	0.92, 1.59
Yes	<29.6	0.97	0.88, 1.06	1.04	0.93, 1.17	1.11	0.88, 1.40	0.99	0.86, 1.13
Yes	≥29.6	1.30	0.91, 1.87	1.39	0.97, 1.98	1.13	0.98, 1.29	1.26	0.86, 1.86
RERI		0.15	−0.08, 0.39	0.16	−0.08, 0.41	−0.01	−0.21, 0.20	0.06	−0.21, 0.34
75th-D2									
No	<29.6	1.00	—	1.00	—	1.00	—	1.00	—
No	≥29.6	1.12	0.87, 1.44	1.13	0.87, 1.45	0.97	0.75, 1.26	1.20	0.94, 1.53
Yes	<29.6	0.97	0.83, 1.12	1.04	0.87, 1.24	1.25	0.92, 1.70	1.03	0.81, 1.30
Yes	≥29.6	1.40	1.01, 1.94	1.47	1.08, 2.00	1.34	1.10, 1.63	1.31	0.96, 1.80
RERI		0.32	−0.01, 0.64	0.31	−0.02, 0.64	0.11	−0.19, 0.42	0.08	−0.28, 0.44
75th-D3									
No	<29.6	1.00	—	1.00	—	1.00	—	1.00	—
No	≥29.6	1.12	0.87, 1.45	1.13	0.87, 1.46	0.96	0.76, 1.21	1.18	0.91, 1.52
Yes	<29.6	0.98	0.84, 1.15	1.06	0.88, 1.28	1.25	0.96, 1.64	1.06	0.82, 1.37
Yes	≥29.6	1.53	1.06, 2.19	1.59	1.13, 2.24	1.43	1.20, 1.71	1.44	0.99, 2.10
RERI		0.42	0.05, 0.79	0.40	0.02, 0.78	0.22	0.00, 0.44	0.20	−0.28, 0.68
75th-D4									
No	<29.6	1.00	—	1.00	—	1.00	—	1.00	—
No	≥29.6	1.17	0.88, 1.55	1.17	0.89, 1.55	1.02	0.83, 1.26	1.22	0.92, 1.62
Yes	<29.6	1.21	1.01, 1.46	1.33	1.06, 1.68	1.25	0.90, 1.74	1.23	0.97, 1.55
Yes	≥29.6	1.63	1.17, 2.26	1.74	1.27, 2.38	1.26	1.05, 1.52	1.52	1.03, 2.25
RERI		0.24	−0.14, 0.63	0.23	−0.19, 0.66	−0.02	−0.35, 0.32	0.08	−0.42, 0.58
90th-D2									
No	<29.6	1.00		1.00		1.00		1.00	
No	≥29.6	1.19	0.91, 1.55	1.19	0.91, 1.55	0.99	0.79, 1.24	1.24	0.94, 1.63
Yes	<29.6	1.32	1.00, 1.76	1.43	1.03, 1.97	1.31	0.87, 1.96	1.52	1.15, 2.00
Yes	≥29.6	1.53	1.13, 2.05	1.59	1.20, 2.10	1.37	1.17, 1.60	1.48	1.07, 2.04
RERI		0.02	−0.47, 0.5	−0.03	−0.56, 0.51	0.07	−0.28, 0.43	−0.28	−0.75, 0.19
95th-D2									
No	<29.6	1.00	—	1.00	—	1.00	—	1.00	—
No	≥29.6	1.21	0.91, 1.62	1.21	0.91, 1.61	0.97	0.77, 1.21	1.25	0.92, 1.68
Yes	<29.6	1.58	1.41, 1.78	1.71	1.46, 2.00	1.28	0.79, 2.06	1.79	1.46, 2.18
Yes	≥29.6	1.55	1.18, 2.03	1.62	1.26, 2.08	1.61	1.27, 2.04	1.50	1.15, 1.95
RERI		−0.24	−0.50, 0.01	−0.30	−0.65, 0.05	0.36	0.08, 0.65	−0.53	−0.91, −0.16
98th-D2									
No	<29.6	1.00	—	1.00	—	1.00	—	1.00	—
No	≥29.6	1.22	0.90, 1.65	1.22	0.91, 1.65	1.02	0.82, 1.26	1.23	0.90, 1.69
Yes	<29.6	2.32	1.48, 3.63	2.59	1.69, 3.98	1.86	1.12, 3.08	2.26	1.35, 3.79
Yes	≥29.6	1.89	1.25, 2.88	2.02	1.31, 3.09	2.18	1.58, 3.01	1.75	1.16, 2.66
RERI		−0.65	−1.67, 0.38	−0.80	−1.89, 0.29	0.30	−0.57, 1.18	−0.74	−2.04, 0.56

Note: —, not applicable; CI, confidence interval; HR, hazard ratio; $PM_{2.5}$, particulate matter <2.5 μm in aerodynamic diameter; PTB, preterm birth; RERI, relative excess risk due to interaction.
[a]Heatwaves were defined by an absolute (33°C) or percentile temperature threshold (75th, 90th, 95th, 98th percentiles, corresponding to 34.6°C, 35.7°C, 36.4°C, and 37°C, respectively) and by the number of consecutive days above the threshold (2–4 d, indicated by D2, D3, or D4). Only nine definitions (33°C-D2, 33°C-D3, 33°C-D4, 75th-D2, 75th-D3, 75th-D4, 90th-D2, 95th-D2, and 98th-D2) were used to allow for sufficient sample size in each subgroup.
[b]The last week average $PM_{2.5}$ was classified as a binary variable using the median of $PM_{2.5}$ concentrations in the last gestational week (29.6 $\mu g/m^3$) as a cut off.
[c]Unadjusted model included only gestational temperature and $PM_{2.5}$ exposures; residency districts of the participants were fitted as a random effect.
[d]Adjusted model additionally included maternal age, parity, month of birth, and relative humidity in the last gestational week before delivery.

(see Table S7), the estimated effects of heatwaves on PTB were similar between vaginal births and Cesarean births. Association between $PM_{2.5}$ during the final gestational week and overall PTB was weaker and still nonsignificant when we adjusted for average $PM_{2.5}$ exposure during weeks 20–28 (see Table S8). When the analyses were stratified by delivery method, the associations of $PM_{2.5}$ during the final gestational week with PTB were positive for both but significant only for Cesarean births (see Table S8).

Discussion

To the best of our knowledge, this study is the first to evaluate both independent effects of heatwave exposure during the last gestational week on PTB and its potential interactive effects with $PM_{2.5}$ exposure. We found that heatwaves, using a number of different definitions, were consistently associated with PTB in our study population. The estimated effects increased with the intensity of heatwaves. For overall PTBs, interaction analyses suggested synergistic effects of $PM_{2.5}$ exposure in combination with less intense heatwaves (i.e., heatwaves defined by a relatively low temperature threshold or fewer consecutive days), but joint effect estimates were less than additive for more intense heatwaves.

In the past few decades, an increasing number of epidemiological studies have evaluated the influence of temperature exposure during pregnancy on PTB (Barreca and Schaller 2019; Carolan-Olah and Frankowska 2014; Guo et al. 2018; Zhang et al. 2017) and other adverse birth outcomes such as birth defects (Soim et al. 2017). Most studies suggested an association between high-temperature exposure during the week prior to the delivery and PTB (Basu et al. 2010; Ha et al. 2017). Relationships between heatwaves (based on an indicator combining both the heat intensity and duration of heat exposure) and PTB have not been studied as extensively. Because there is no universal definition of a heatwave, two previous studies of PTB have used a series of cut off temperatures and durations to define heatwaves (Kent et al. 2014; Wang et al. 2013). One U.S. study, in Alabama, observed mixed results, including positive, negative, and null associations between heatwave events and PTB at 0- or 1-d lags (Kent et al. 2014). Another study of heatwave exposures during the final week before delivery reported a robust association between heatwaves under different definitions and PTB in Brisbane, Australia (Wang et al. 2013). Similar to the study in Brisbane, we used 12 different definitions and found most heatwaves were associated with greater risk of PTB. Moreover, associations were stronger for longer heatwaves with the same temperature threshold as well as for heatwaves defined by higher temperature thresholds but the same duration.

When examined by gestational age, most heatwaves were associated with a higher risk of PTB at 35–36 weeks and only very intense heatwaves (95th-D2, 95th-D3, 98th-D2) were associated with PTB at 28–34 weeks. A possible explanation is that environmental stressors are more likely to contribute to later PTB, whereas nonenvironmental factors are more responsible for earlier PTB. Previous studies have suggested that infection is the most important factor for extreme PTB (<28 weeks), whereas environmental stressors and lifestyle factors accounted for mild PTB (32–36 weeks) and a mixture of environmental stressors, lifestyle factors, and infection contributed to very PTB (28–32 weeks) (Moutquin 2003).

It is plausible that extreme temperatures would act synergistically with air pollution to affect health (Gordon et al. 2014; Li et al. 2014; Tian et al. 2014), and some empirical studies have reported evidence of interactive effects on mortality or hospitalization rates (Benmarhnia et al. 2014; De Sario et al. 2013; Li et al. 2017; Shaposhnikov et al. 2014). However, the combined effects of heat and air pollution on PTB have not been studied previously. In this research, we assessed additive-scale interactions between heatwaves and $PM_{2.5}$ on PTB and observed some notable interaction patterns. Estimated effects of combined exposure to higher $PM_{2.5}$ and less intense heatwaves (i.e., heatwaves with relatively low temperature thresholds or with fewer consecutive days) were more than additive for overall, earlier, and later PTBs. Previous studies reported an increase in PM toxicity at higher temperatures and heat stress may increase the uptake of air pollutants in the human body through sweating, elevation in skin blood flow, and minute ventilation (Gordon et al. 2014), which may be part of the underlying mechanisms. Joint effects for $PM_{2.5}$ and more intense heatwaves appeared to be less than additive (RERIs <0), especially for very intense heatwaves (daily maximum temperature $\geq 35.7°C$ (the 90th percentile) and lasting for at least 3 or 4 d, daily maximum temperature $\geq 36.4°C$ (the 95th percentile) for at least 2 or 3 d, $\geq 37°C$ (the 98th percentile) for 2 d), indicating that the joint effects were less than expected based on the estimated independent effects for each exposure. We considered that this may be due, at least in part, to behavioral changes. Under extremely high temperatures, mothers are more likely to attempt to mitigate exposure, including altering clothing, drinking fluids, or using air conditioning (Carolan-Olah and Frankowska 2014; Liang et al. 2016). Such adjustments may offset some of the harmful effects of very intense heatwaves. Moreover, people tend to reduce outdoor activities during very hot days, thereby potentially reducing their exposure to both heatwaves and $PM_{2.5}$.

The main strength of our study is that we treated gestational age as a time-to-event variable and performed a survival analysis to estimate short-term effects. This approach accounts for the impacts of time-varying gestational temperature and $PM_{2.5}$ exposure and also accommodates differences in exposure length among pregnancies of different gestational ages, thereby enabling us to detect the effect of each exposure in the gestational week preceding delivery.

This study has several potential limitations. We used district-specific meteorological factors and air pollution to assign individual exposure for all women during their pregnancy. Exposure misclassification could be present due to the lack of information on the exact residential address, maternal activity patterns, and residential mobility during pregnancy. Moreover, we were unable to estimate the effects of heatwaves or air pollution on spontaneous and medically indicated PTB subtypes due to the lack of this information in our data. However, we stratified analyses by vaginal and Cesarean delivery mode, which are related to PTB subtype. We also did not use multipollutant models because of the moderate-to-high correlation between air pollutants in this study. Therefore, the potential confounding by other pollutants could not be assessed. Further, we were unable to consider several potentially important modifying factors, including the presence of cervicovaginal or intrauterine infections, specific prenatal complications (preeclampsia, eclampsia, gestational diabetes mellitus), socioeconomic status, maternal exercise, smoking, and nutritional status because these variables were not available in the birth registry system. Finally, we treated heatwave exposure as a binary variable without considering the number of heatwaves because the exposure window we focused on (the final gestational week before delivery) was relatively short and very low numbers of pregnant women experienced more than one heatwave during this brief window.

Conclusions

This study strengthens the evidence that exposure to heatwaves late in gestation can independently trigger preterm birth. Our novel findings of interactive effects suggest that moderate heatwaves act synergistically with $PM_{2.5}$ exposure on the risk of preterm birth. This adds new evidence to the current understanding of the combined effects of air pollution and meteorological variables on adverse birth outcomes. However, we did not see evidence of synergistic effects of $PM_{2.5}$ exposure and more intense heatwaves, possibly due to effective behavioral adaptations in extremely hot days. In the context of climate change, our results underscore the potential co-benefits of mitigating women's exposure to hot weather and air pollution during pregnancy.

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